Original Article

Bacterial mitigation strategies: impact of pathogen reduction and large-volume sampling on platelet productivity

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Background: As blood centers evaluate strategies to further mitigate the risk of bacterial contamination and septic transfusion reactions associated with platelets, modeling provides valuable information in terms of impact to apheresis platelet productivity. A real-world donor database was used to model platelet productivity to provide a comparison of large-volume delayed sampling (LVDS) and pathogen reduction (PR) as well as platelet transfusion dose.

Methods: A model, based on the algorithms that predict donor qualification on the Trima Accel Automated Blood Collection System, was developed to analyze large donor populations to predict platelet productivity. Modeling was performed with Trima Accel software version 6 and version 7 for platelets stored in plasma and platelets stored in 65% platelet additive solution (PAS). The model was used to calculate the number of platelet units collected per completed apheresis procedure (PPP) for the following scenarios: (I) blood centers target 100% of their platelet inventory to undergo LVDS; (II) blood centers target 50% of their platelet inventory to undergo PR (with the INTERCEPT Blood System or the Mirasol Pathogen Reduction Technology system) and the other 50% LVDS; (III) blood centers target 100% of their platelet inventory to undergo PR, and any units that do not fall into PR specification ranges undergo LVDS. Scenarios were run with three platelet transfusion doses: 3.0, 2.5 and 2.0×10^{11}.

Results: PPP was lower for the INTERCEPT arm compared to LVDS and Mirasol due to the restrictions in INTERCEPT treatment specification ranges and platelet loss experienced during the chemical adsorption step. PPP decreased as the percentage of inventory targeted for INTERCEPT treatment increased. PPP was higher on Trima Accel version 7 compared to version 6. PPP was higher for platelets stored in plasma compared to platelets stored in PAS because platelets in plasma can be collected at higher flow rates. Lower platelet transfusion doses yielded higher PPP.

Conclusions: The transition to more stringent bacterial mitigation strategies results in a decrease in apheresis platelet productivity in all scenarios. The increase in platelet productivity realized on Trima Accel version 7 can help blood centers maintain platelet availability with either LVDS or PR.

Keywords: Bacterial mitigation strategies; platelet availability; pathogen reduction (PR); large-volume delayed sampling (LVDS)

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Introduction

Bacterial contamination of platelets is the leading risk for transfusion-transmitted infections in developed nations (1,2). Regulatory agencies and blood centers around the world continue to take strides to further mitigate this risk. In August 2017, Canadian Blood Services adopted large-volume delayed sampling (LVDS) to decrease the risk of bacterial contamination while also increasing platelet shelf life from 5 days to 7 days (3). The algorithm adopted by Canadian Blood Services is similar to the algorithm pioneered by the National Health Service Blood and Transplant (U.K.) in 2011 (3,4). In September 2019, the United States Food and Drug Administration (U.S. FDA) released the final guidance titled "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion" which was later updated in December 2020 (1). In this guidance, the FDA outlines single-step and two-step strategies to enhance the safety of the U.S. platelet supply. Single-step strategies include LVDS and pathogen reduction (PR), whereas two-step strategies require primary and secondary testing over the course of platelet shelf life. According to a survey by Lu *et al.*, 72% of hospital-based transfusion services in the U.S. prefer the single-step strategies outlined in the U.S. FDA guidance document compared to the two-step strategies (5).

One of the primary challenges identified with the single-step strategies is the impact on platelet productivity based on the number of transfusable units that can be produced and ultimately on platelet availability (6,7). In the case of PR, platelet targets and lab minimums must be adjusted to accommodate the treatment specification ranges of PR systems, which impact platelet productivity. LVDS also affects productivity, because a larger volume must be removed from the platelet collection (at least 16 mL per unit or daughter bag compared to the current sampling method of 8 mL per mother bag) for testing (1). Another variable that affects platelet availability is the transfusion dose, which is between 2.0 and 3.0×10^{11} platelets per unit depending on the country (8). Lowering the transfusion dose from common practice will increase the number of transfusable units that can be collected per donor (8).

The purpose of this study was to model the impact of single-step bacterial mitigation strategies (PR, LVDS) and various platelet transfusion doses on platelet productivity using a real-world donor database.

We present the following article in accordance with the TREND reporting checklist (available at http://dx.doi.org/10.21037/aob-21-19).

Methods

Terumo Blood and Cell Technologies has developed a model to evaluate large data sets of donor populations. This model is based on algorithms from the Trima Accel Automated Blood Collection System software that calculate whether a donor qualifies to donate a single, double, or triple platelet collection based on gender, height, weight, and pre-donation platelet count. Modeling was performed using algorithms from Trima Accel software version 6 and version 7 for platelets stored in plasma and platelets stored in 65% platelet additive solution (PAS). Historical lab data comparing Trima Accel predicted platelet yield and volume with actual (lab-measured) platelet yield and volume was used to adjust the model to match real-world experience (i.e., account for a proportion of triple collections falling short of target yield and counted as double collections, and double collections falling short of target yield and counted as single collections). The model was used to predict platelets per procedure (PPP) calculated as the total number of transfusable platelet units that could be collected from a donor database divided by the total number of completed apheresis procedures.

Donor database

The donor database is a compilation of 10,000 platelet donors representing donor demographics from three major blood centers in the U.S. The model was run for transfusion doses of 3.0, 2.5, and 2.0×10^{11} per unit.

Lab minimums

For the transfusion dose of 3.0×10^{11}: 3.0×10^{11} counted as a single, 6.2×10^{11} counted as a double, and 9.3×10^{11} counted as a triple. For the transfusion dose of 2.5×10^{11}:2.5×10^{11} counted as a single, 5.2×10^{11} counted as a double, and 7.8×10^{11} counted as a triple. For the transfusion dose of 2.0×10^{11}: 2.0×10^{11} counted as a single, 4.2×10^{11} counted as a double, and 6.3×10^{11} counted as a triple. INTERCEPT modeling included subtraction of 10% platelet volume and yield from the collection prior to splitting due to the chemical adsorption step (9). Because this 10% platelet volume and yield loss was subtracted from the INTERCEPT collection before splitting, INTERCEPT

Table 1 Configuration of Trima Accel targets for platelet yield and platelet volume applied to model for LVDS and PR

Targets	Platelet yield (platelets $\times 10^{11}$)	Platelet volume (mL)
Triple platelet collection (LVDS, PR)	11	700
	10.8	680
	10.5	680
	10.2	650
Double platelet collection (LVDS, PR)	7.9	600
	7.4	580
	7	580
Double platelet collection (PR only)	7	400
	6.8	400
Single platelet collection (LVDS, PR)	4.2	315

LVDS, large-volume delayed sampling; PR, pathogen reduction.

platelets were subject to the same lab minimums described above.

Regarding PR, the model included platelet yield and volume targets optimized to fit into the respective INTERCEPT treatment specification ranges (i.e., guard bands). For triple collections, the INTERCEPT arm utilized splitting triple collections into a treatable double product and single product. For double collections, the INTERCEPT arm utilized an equal mixture of one double storage (DS) and two single volume/large volume (SV/LV) options to treat doubles depending on whether the product met the treatment specifications for each kit. The INTERCEPT arm did not include volume mitigation or variable dose strategies; volume mitigation is the removal of volume from the platelet product to fit into the specification range, and variable dose is allowing transfusion doses below the allowable transfusion dose (7,10). The Mirasol arm utilized splitting double and triple collections into treatable singles

Bacterial mitigation strategies

The current sampling method consists of removing 8 mL per mother bag for bacterial culture testing. LVDS consists of removing 16 mL per daughter bag for bacterial culture testing. Modeling of PR platelets was targeted to meet platelet yield and volume specifications (i.e., guard bands) for two PR technologies: the INTERCEPT Blood System (Cerus Corporation, Concord, USA) and the Mirasol Pathogen Reduction Technology System (Terumo Blood and Cell Technologies, Lakewood, USA) (11-13). The Mirasol system is available in select countries under CE Mark or local regulatory approval; Mirasol is not approved for use in the U.S. If a PR platelet target did not qualify for the respective PR disposable set specification, the product was treated as an LVDS product and the removal of 16 mL per daughter bag was calculated into the final product. Trima Accel targets were established to optimize PPP for LVDS and INTERCEPT as well as to optimize the number of platelet products that qualified for INTERCEPT treatment; the same targets were used for Mirasol to maintain a consistent comparison (*Table 1*).

Assumptions

The model assumes an accurate pre-donation platelet count is entered into the Trima Accel system, which requires the donor platelet count to be measured before the apheresis procedure on the day of collection. Entering same day platelet count is considered best practices as described in the Trima Accel operator's manual (14). The model also assumes that the operator selects the highest number of platelets offered by the device for all collections which represents best case. All procedures used in the model were run to completion and the respective donor was used only once per modeling exercise to calculate the potential productivity of the donor population independent of donor behavior. For the scenario where 50% of platelet inventory was PR-treated, procedures chosen for PR treatment were randomly selected to maintain comparability.

Table 2 Summary of donor demographics for 10,000 donors representing U.S. blood centers

Donor	% Split	TBV (mL)		Platelet pre-count (×10^3 platelets per µL)		HCT (%)	
		Average	Std Dev	Average	Std Dev	Average	Std Dev
Female	31%	4,469	711	287	57	40.6	2.2
Male	69%	5,728	758	255	51	43.7	3.0
Total		5,343	943	265	55	42.8	3.1

Results

Donor demographics used for the modeling are summarized in *Table 2*. The donor database population was 31% female, with an average total blood volume of 4,469 mL and average platelet pre-count of 287×10^3 platelets per µL; and 69% male, with an average total blood volume of 5,728 mL and average platelet pre-count of 255×10^3 platelets per µL.

Platelet productivity

Table 1 summarizes the platelet yield and volume targets configured in the Trima Accel device to determine whether a donor qualified to donate single, double, or triple platelet units. Targets for platelet yield and volume were optimized to ensure the highest PPP for LVDS and INTERCEPT and to ensure the optimum number of platelet products qualified for treatment with the INTERCEPT system. Target volume was increased for all targets to account for increased sample volumes. Lab minimums used to determine whether a donation qualified as a single, double, or triple are described in the Methods section.

The results from the model are presented in *Table 3* in terms of PPP or split rate. Blood centers use PPP as a metric of productivity: the higher the PPP, the higher the productivity. A split rate of two means that on average, every apheresis collection yields two platelet products. *Table 3* presents data for three different scenarios: (I) blood centers target 100% of their platelet inventory to undergo LVDS; (II) blood centers target 50% of their platelet inventory to undergo PR and the other 50% LVDS; (III) blood centers target 100% of their platelet inventory to undergo PR, and any units that do not fall into the PR specification ranges undergo LVDS.

In all scenarios, PPP decreased compared to the current bacterial sampling method of 8 mL per mother bag. LVDS removed a larger volume from each daughter bag; thus fewer platelet collections qualified as doubles or triples, which decreased PPP. However, implementation of 100% LVDS with Trima Accel version 7 resulted in higher PPP compared to the current 8 mL bacterial sampling method with Trima Accel version 6 for platelets in plasma. This was not the case for platelets in PAS; collection of concentrated platelets to be stored in PAS required slower flow rates, resulting in lower PPP compared to platelets in plasma.

The scenario of 100% LVDS resulted in higher PPP compared to using INTERCEPT to treat 50% or 100% of platelet inventory. In general, PPP decreased as the percentage of inventory targeted for INTERCEPT treatment increased. Each PR system has specification ranges in terms of platelet yield and volume. Only products that fall into the specification ranges (either as singles, doubles, doubles split into singles, or triples split into singles and doubles) qualify for PR treatment. The model does not include volume mitigation. In the case of INTERCEPT, the treatment specification ranges in addition to the 10% loss in platelet volume and yield during the chemical adsorption step resulted in lower PPP (9).

PPP for Mirasol was lower compared to the current sampling method because the model included Trima Accel collection targets optimized for LVDS and INTERCEPT. Collection targets were not optimized for Mirasol in order to maintain consistent settings with LVDS and INTERCEPT scenarios. Mirasol resulted in higher PPP compared to INTERCEPT because Mirasol has wider treatment specification ranges and is not associated with the 10% loss in platelet volume and yield that occurs with the INTERCEPT chemical adsorption step. PPP for Mirasol was also higher than that for LVDS because Mirasol does not include removal of 16 mL per daughter bag. None of the scenarios reached 100% of platelet inventory qualifying for PR treatment; however, more products qualified for treatment in the Mirasol arm compared to the INTERCEPT arm for all three of the platelet doses evaluated.

Table 3 PPP calculated for bacterial mitigation strategies including 100% LVDS, 50% PR and 50% LVDS, and 100% PR. PR modeled for the INTERCEPT Blood System and the Mirasol PRT System (not approved for use in the U.S.)

Platelets per procedure (PPP)	Current sampling method	Target 100% LVDS and 0% PR	Target 50% PR and 50% LVDS				Target 100% PR with units that fail to qualify undergoing LVDS			
			INTERCEPT	Percentage units qualify for INTERCEPT treatment	Mirasol	Percentage units qualify for Mirasol treatment	INTERCEPT	Percentage units qualify for INTERCEPT treatment	Mirasol	Percentage units qualify for mirasol treatment
Platelet dose =3.0×10^{11}										
Trima Accel Version 6 (platelets in plasma)	2.12	2.02	1.96	39%	2.05	44%	1.90	80%	2.07	87%
Trima Accel Version 7 (platelets in plasma)	2.30	2.20	2.14	39%	2.22	46%	2.08	80%	2.24	91%
Trima Accel Version 7 (platelets in PAS)	2.19	2.09	2.02	32%	2.22	46%	1.95	66%	2.24	91%
Platelet dose =2.5×10^{11}										
Trima Accel Version 6 (platelets in plasma)	2.41	2.30	2.27	40%	2.33	44%	2.24	80%	2.37	87%
Trima Accel Version 7 (platelets in plasma)	2.59	2.48	2.45	40%	2.50	46%	2.42	80%	2.51	91%
Trima Accel Version 7 (platelets in PAS)	2.51	2.39	2.34	33%	2.50	46%	2.28	67%	2.51	91%
Platelet dose =2.0×10^{11}										
Trima Accel Version 6 (platelets in plasma)	2.70	2.61	2.57	40%	2.63	46%	2.54	81%	2.65	90%
Trima Accel Version 7 (platelets in plasma)	2.82	2.76	2.73	40%	2.78	48%	2.69	81%	2.79	96%
Trima Accel Version 7 (platelets in PAS)	2.79	2.72	2.65	34%	2.78	48%	2.58	70%	2.79	96%

LVDS, large-volume delayed sampling; PR, pathogen reduction; PAS, platelet additive solution.

Overall, PPP for platelets collected on Trima Accel version 7 was higher than for those collected on version 6 for all scenarios. On average, PPP was 7% higher on version 7 compared to version 6.

Platelet dose

The model was used to predict the impact of various platelet doses on platelet productivity. Lowering the platelet dose from 3.0 to 2.5×10^{11} resulted in an average 15% increase in PPP. Lowering the platelet dose from 3.0 to 2.0×10^{11} resulted in an average 28% increase in PPP. Procedure targets were not adjusted to account for lower dose in order to maintain comparability.

Limitations

Limitations to the model included minimal changes to Trima Accel targets to maintain comparability. There are improvements that could have been made with LVDS, Mirasol, and lower yield settings that would have yielded even higher PPPs. The model also assumed the most conservative usage for INTERCEPT disposable sets (e.g., modeling preferred use of one DS set over two SV sets).

Discussion

As blood centers evaluate strategies to further mitigate the risk of bacterial contamination and septic transfusion reactions associated with platelets, modeling using a common donor database provides valuable information about platelet productivity after implementation of LVDS and PR at different platelet transfusion doses.

Although all bacterial mitigation strategies result in a decrease in PPP compared to the current sampling method, Trima Accel version 7 allows blood centers to regain platelet productivity. Trima Accel software version 7 was upgraded with algorithms that optimize flow rate and interface management to improve platelet productivity. The 7% increase in PPP with version 7 compared to version 6 modeled herein matches routine-use experience by U.S. blood centers reporting an increase of 4% to 11% (15-17). Trima Accel version 7 with platelet mobilization algorithm has not been evaluated for splenectomized donors (14).

Another factor to be considered is whether to store platelets in plasma or PAS. Collecting platelets in PAS is associated with lower PPP compared to plasma because collection of platelets in PAS on Trima Accel requires slower flow rates. In Europe, INTERCEPT is frequently used in combination with Trima Accel and PAS. In the U.S., the INTERCEPT system is approved by the FDA only for platelets collected on the Trima Accel system and stored in plasma.

In the U.S., blood centers are considering a mix of PR and LVDS. It should be noted that without significant manipulation of the products themselves, blood centers cannot treat 100% of their platelet inventory. For the transfusion dose of 3.0×10^{11}, the maximum percentage of units qualifying for treatment with the INTERCEPT system calculated in this model was 75%. This value is consistent with a previous study which calculated between 73% and 81% but included volume mitigation (7). Several studies have modeled that blood centers can approach 100% of platelet inventory qualifying for PR with the INTERCEPT system by adopting a variable dose strategy (7,10). This strategy specifies that a certain percentage of platelet products in inventory contain less than the required dose for transfusion. Previous studies define variable dose from the standard U.S. dose of 3.0×10^{11} down to 2.2×10^{11} in order to achieve 100% PR (7,10).

Different countries around the world use different platelet doses ranging from 2.0 to 3.0×10^{11} (8). Lowering the platelet dose from 3.0 to 2.5×10^{11} in the US would increase PPP by 15%. This value is lower than the 21% reported by Benjamin *et al.* that was based on a single U.S. blood center using Trima Accel (8). For a large blood center that collects 50,000 apheresis platelet units per year, an increase in PPP by 15% translates to 7,500 additional doses. Lower transfusion doses are supported by the PLADO study, which evaluated the impact of platelet dose on bleeding in stable hematology-oncology patients (18). There was no increase in incidence of bleeding in the patient population receiving the lower platelet dose (roughly 2.1×10^{11}); however, the lower-dose arm was associated with an increase in the number transfusions per patient (8,18). Although lowering the transfusion dose would result in an immediate increase in platelet availability, long-term there could be an increase in demand due to more frequent transfusion. Moreover, the PLADO study included only stable non-bleeding patients (18). Similar studies should be repeated in different patient populations, including actively bleeding or hemorrhaging patients, before unanimously changing transfusion dose.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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